Transmission of Multidrug-Resistant *Mycobacterium tuberculosis* During a Long Airplane Flight.

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Abstract

Background: In April, 1994 a passenger with infectious multidrug- resistant tuberculosis traveled on commercial-airline flights from Honolulu to Chicago and from Chicago to Baltimore and returned one month later. We sought to determine whether she had infected any of her contacts on this extensive trip.

Methods: Passengers and crew (contacts) were identified from airline records and were notified of their exposure, asked to complete a questionnaire, and screened by tuberculin skin tests.

Results: Of the 925 people on the airplanes, 802 (86.7 percent) responded. All 11 contacts with positive tuberculin skin tests who were on the April flights and 2 of 3 contacts with positive tests who were on the Baltimore-to-Chicago flight in May had other risk factors for tuberculosis. More contacts on the final, 8.75-hour flight from Chicago to Honolulu had positive skin tests than those on the other three flights (6 percent, as compared to 2.3, 3.8, and 2.8 percent). Of 15 contacts with positive tests on the May flight from Chicago to Honolulu, 6 (4 with skin-test conversions) had no other risk factors; all 6 had sat in the same section of the plane as the index patient (P=0.001). Passengers seated within two rows of the index patient were more likely to have positive tuberculin skin tests than those in the rest of the section (4 of 13, or 30.8 percent, vs. 2 of 55, or 3.6 percent; rate ratio, 8.5; 95 percent confidence interval, 1.7 to 41.3; P=0.01).

Conclusions: The transmission of *Mycobacterium tuberculosis* that we describe aboard a commercial aircraft involved a highly infectious passenger, a long flight, and close proximity of contacts to the index patient. (N Engl J Med 1996;334:933–8.)

Background

A 1993 investigation of a flight attendant with infectious tuberculosis demonstrated transmission to other crew members, but evidence of transmission to passengers was inconclusive.[1] In June, 1994, the Centers for Disease Control and Prevention (CDC), was notified by a state health department that a visitor from a foreign country had died of complications from pulmonary tuberculosis; her *Mycobacterium tuberculosis* isolate was resistant to isoniazid, rifampin, pyrazinamide, streptomycin, and kanamycin. Prior to diagnosis in May, 1994 she flew from Honolulu to Chicago to Baltimore in April, 1994 and returned one month later. Because of the extent of her disease, concern for potential transmission of drug-resistant *M.tuberculosis*, and uncertainty regarding passenger to passenger transmission of *M.tuberculosis* on aircraft, an investigation of passengers and flight crew was conducted. The results of this investigation prompted the CDC to issue recommendations concerning notification of passengers and flight crew following exposure to tuberculosis on an aircraft.[2]

Methods

Investigation of Index Case and Household Contacts

Medical and laboratory records of the index case were reviewed. State and local health departments completed contact investigations of the two households in the two states where the index case had lived during her visit to the United States.

Investigation of Flight Crew and Passengers

The passenger manifest and list of flight crew for the four flights were obtained from the airline company. Information from the manifest and from frequent flyer records was used to locate passengers and identify seat assignments. Persons who were not residents of the United States or Canada were excluded from the investigation. Passengers and flight crew (referred to as contacts) were notified of their potential exposure to tuberculosis by certified letter, advised to have a Mantoux tuberculin skin test, and asked to complete a questionnaire. Data collected included demographic and epidemiologic information. Except for contacts with evidence of prior tuberculosis or a prior positive tuberculin skin test, skin test results were based on written records provided by the health department or personal physician.

Contacts with a negative tuberculin skin test performed less than 12 weeks after the flight were mailed a second letter advising them of the need for a final test at least 12 weeks post-exposure. A prevalent positive tuberculin skin test was defined as 10 mm of induration or greater. Tuberculin skin test conversion was defined as 10 mm or greater increase in induration within the previous two years. Contacts with a positive tuberculin skin test or conversion were interviewed concerning other risk factors for

tuberculosis. Tuberculin skin test and interview results were independently reviewed by three tuberculosis experts who made an assessment whether positive results were due to new infection or boosting.[3-5]

Data Analysis

Tuberculin skin test results were analyzed by age, sex, race and ethnicity, flight, flight duration, and seat proximity to the index case. Categorical variables were compared using the chi-square or Fisher exact test. Continuous variables were compared using the Student's t-test.[6]

Aircraft

Information about the type of aircraft flown on each flight was obtained from airline records. Airline industry diagrams were used to map seat assignments and manufacturers' specifications of airflow and air distribution systems were reviewed for each type of aircraft. Aircraft ventilation systems were not evaluated otherwise.

Results

Index Case

The index case was a 32 year old female Korean national who, according to relatives, was on no anti-tuberculous medication but had been previously treated for tuberculosis twice as an adolescent in Korea and once within the past two years in Japan with unknown medication. She arrived in Honolulu in April on a tourist visa and, reportedly, had cough and lethargy while staying with friends (Household 1) for five days. She then flew from Honolulu to Chicago and Chicago to Baltimore, where she remained with friends (Household 2) for one month. Members of household 2 reported worsening of her symptoms, including progressive cough, lethargy, shortness of breath, fever, night sweats, and the eventual onset of scant hemoptysis. In May, she returned to Honolulu, flying from Baltimore to Chicago, and Chicago to Honolulu. Eight days after returning to Household 1, she experienced an acute episode of hemoptysis, described as consisting of approximately one liter of bright red blood. Hospital evaluation revealed extensive pulmonary disease (Figure 1) and her sputum was highly (3+) positive for acid-fast bacilli (AFB) and culture positive for *M.tuberculosis*. The patient died from pulmonary hemorrhage and respiratory failure five days after hospitalization.

Household Contacts of Index Case

Both Korean-born parents in Household 1 were tuberculin skin test positive in June, 1994. Their two children, ages 3 and 7 years, were both skin test negative at 14 weeks post-exposure. The mother in Household 2 had a prior positive skin test in 1977

and her chest film was negative in May, 1994. The father's test demonstrated 12 mm of induration the end of May and his chest film was negative. Their 21 month old U.S.-born child's tuberculin skin test converted from 0 mm of induration in May and early July (two and eight weeks after departure, respectively) to 22 mm of induration at 17 weeks after the index case departed. As of December, 1995, he remained free of signs and symptoms of active tuberculosis.

Flight Crew and Passengers

Of 1,042 passenger and crew contacts identified on the four flights, 117 (11.2 percent) were not notified: 24 were residents of foreign countries and 93 had no locating information. The remaining 925 (88.8 percent) resided in 41 states, Puerto Rico, the District of Columbia, and Canada and were notified of their potential exposure. Of these, 802 (86.7 percent) provided final tuberculin skin test results. Forty-two contacts were excluded from analysis; 40 had prior tuberculosis or evidence of a prior positive tuberculin skin test, one died of cancer, and one died of AIDS with documented anergy. Neither contact who died developed signs and symptoms compatible with tuberculosis. The passenger with AIDS was already on rifabutin prophylaxis and had negative AFB smears and cultures following exposure.

Of the 760 contacts analyzed, 95 percent were passengers and 5 percent were crew members. Only 10 (1.3 percent) contacts were exposed on two connecting flights. Fifty-five percent of contacts were male, 94 percent were U.S.-born, 86 percent were white, and the median age was 43 years (range 6 months to 86 years). There were no statistically significant differences in the demographic characteristics of contacts among the four flights. Prior Bacille Calmette Guerin (BCG) vaccination and exposure to a family member or friend with tuberculosis was reported by 2.6 percent and 7.5 percent of all contacts, respectively.

Results of tuberculin skin test screening of contacts are shown in Table 1. None of the contacts with a prevalent positive tuberculin skin test had results of prior tests in their medical record. The first tuberculin skin test for the six contacts with conversion on Flight 4 was performed a median of 8 weeks post-exposure (range 34 weeks pre-exposure to 10 weeks post-exposure) and the second test was administered a median of 23 weeks post-exposure (range 8 to 29 weeks). All contacts with a negative tuberculin skin test had a final test performed at least 12 weeks post-exposure (median 16 weeks, range 13 to 32 weeks).

All 11 contacts on Flights 1 and 2 with a positive tuberculin skin test had other risk factors, including birth in a foreign-country where tuberculosis is highly endemic[7] or receipt of BCG (n=5), exposure to tuberculosis in a family member (n=3), residence overseas (n=2), or occupational exposure (n=1). Passengers on Flights 1 or 2 with a positive tuberculin skin test were not seated near the index case. On Flight 3, three persons had positive tuberculin skin tests, but none had conversion. Of these, two were born in countries where tuberculosis is highly endemic and had received BCG. Other

risk factors for tuberculosis were denied by the third person with a positive tuberculin skin test, who was seated three rows away from the index case.

The characteristics of the 15 contacts on Flight 4 with a positive tuberculin skin test are included in Table 2 and their seat assignment in relationship to the index case is illustrated in Figure 2. The index case was seated next to the aisle in the second to last row of the rear cabin section of the aircraft. Nine contacts with a positive tuberculin skin test had other tuberculosis risk factors identified, and were seated throughout the aircraft. Six contacts with a positive tuberculin skin test, including four with conversion, had no other tuberculosis risk factors identified.

Table 3 summarizes the association between tuberculin skin test results and seating proximity to the index case for contacts on Flight 4 with no other risk factors identified. Compared with contacts who had a negative tuberculin skin test, contacts with a positive test, including four with conversion, were more likely to be seated in the same cabin section of the aircraft as the index case (P=0.001). In fact, all six contacts with a positive tuberculin skin test and no risk factors, including all four with conversion, were seated in the same cabin section of the aircraft as the index case. Those seated within two rows of the index case were 8.5 times more likely to have a positive tuberculin skin test or conversion than those seated elsewhere in the same cabin section. Among the six persons with a positive tuberculin skin test, four were seated within two rows of the index case and the two seated towards the front of the rear cabin section reported frequently visiting friends seated very near the index case and used the lavatory close to the seat of the index case. As of February, 1996, all six remain free of signs and symptoms of active tuberculosis.

Aircraft and Ventilation Systems

For both trans-oceanic flights, Flights 1 and 4, Boeing 747-100 aircraft were used. These flights were 8 hours and 8.75 hours duration in April and May, respectively. The Chicago-Baltimore and Baltimore-Chicago flights, Flights 2 and 3, were both on Airbus 320-200 aircraft and were 1.75 and 2 hours duration, respectively. No flight delays were reported to have occurred on any of the flights. Both the B747-100 and A320-200 aircraft had air recirculation systems with high efficiency particulate air (HEPA) filtration. The B747-100 aircraft recirculates air through one common reservoir for the entire aircraft. Approximately 50 percent of the air is recirculated and air exchange rates reported by the manufacturers of these types of aircraft range from six to 20 times per hour. Smoking was prohibited on all four flights.

Discussion

This incident provided a unique opportunity to investigate *M. tuberculosis* transmission on aircraft. A high proportion of U.S. residents, repeated notification, and national media attention facilitated achievement of a high response rate among

contacts. Prompt notification by a state tuberculosis control program allowed prospective assessment of the development of tuberculous infection in the May, 1994 passengers and flight crew.

This investigation provides evidence of passenger to passenger and flight crew transmission of *M.tuberculosis* aboard commercial aircraft. Though the possibility of transmission from the index case to other passengers on Flights 1, 2, and 3 cannot be excluded, the evidence is most compelling for Flight 4. This includes evidence of recent transmission (i.e., skin test conversions), an association between transmission and proximity to the index case, and a dose-response effect. All but one of the contacts who had no risk factors for tuberculosis and a positive skin test, including all with conversion, were seated in the same section as the index case and those seated within two rows were at greatest risk. The tuberculin skin test conversions on Flight 4 but not on Flight 3 on the same day suggests prolonged exposure to aerosol droplets from the index case played a role. The apparent lack of transmission on Flight 1 may have been due to varying infectiousness of the index case who had longstanding disease. She was more symptomatic in May than in April. The timing of skin test conversion in the child in Household 2 suggests transmission occurred just prior to Flights 3 and 4. The children in Household 1 may have escaped infection because the index case was less infectious in April, they were not in close proximity to her when she returned in May, or due to chance alone since many household contacts of a person with infectious tuberculosis are known to remain uninfected.[8,9] Since no clinical data exist on the risk and benefits of preventive therapy regimens that do not include isoniazid and rifampin, clinicians of infected contacts had two options: a) administer no preventive therapy and provide careful clinical follow-up for the appearance of signs and symptoms of tuberculosis,[10] or b) consider six months of preventive therapy with rifabutin to which the isolate was fully susceptible.

These findings are consistent with previous reports of transmission of other airborne pathogens on commercial aircraft, such as measles, influenza, and smallpox.[11-13] Our results are also consistent with the previous finding that the risk of *M. tuberculosis* transmission from a flight crew member with infectious tuberculosis to other crew members increased with duration of in-flight hours of exposure.[1] Previous investigations involving closed environments, including naval ships, also showed an association between proximity to a person with infectious tuberculosis and transmission of *M.tuberculosis*.[14] In our investigation, the lack of tuberculin skin test conversions in other cabin sections of the aircraft on Flight 4 further suggests that *M.tuberculosis* was not transmitted through the aircraft's air recirculation system.

Domestic air travel in the United States increased by 62 percent from 1980 through 1993, from 275 million to 445 million passengers per year.[15] Air travel from foreign countries to the United States also increased by 180 percent from 12.6 million passenger arrivals during 1975 to 35.5 million in 1991.[15] The World Health Organization's projections for the worldwide tuberculosis epidemic include 90 million new cases during the present decade.[16] Increases in air travel, tuberculosis worldwide,

and immigration to the United States from countries with high rates of tuberculosis imply that exposure of passengers to persons with tuberculosis on commercial aircraft can be anticipated.[15-17]

Following reports of this incident in the national media during July, 1994, CDC received unsolicited reports of another 30 airline passengers with tuberculosis, including 10 whose diagnosis was already known at the time of travel, who were on commercial flights from July through December, 1994. Assuming approximately 260 million airline passengers during the July-December, 1994 time period, these 30 passengers with tuberculosis are estimated to represent approximately one out of every 9 million passengers.[15] This probably underestimates the risk of exposure to tuberculosis on aircraft since reporting was unsolicited and likely to be incomplete. However, assuming 300 passengers per international flight and 150 per domestic flight, as many as 10,000 passengers may have been exposed to *M.tuberculosis* on these flights, or approximately one out of every 26,000 passengers who flew during this time period. Furthermore, less than one percent of all contacts from our investigation had a tuberculin skin test conversion as a result of exposure to the index case on the aircraft. Though limited by under-reporting, these data suggest a relatively low risk for exposure to, and transmission of, *M.tuberculosis* to passengers and crew on commercial aircraft in the United States.

In this investigation, the passenger with tuberculosis was a tourist from a region of the world where tuberculosis is highly endemic.[7,16] Screening for active tuberculosis is required for immigrants and refugees applying for legal status in the United States, but not for nonimmigrant arrivals such as tourists, visitors on business, and students.[18] During 1993, 79 percent of the 21.4 million nonimmigrant arrivals in the United States were tourists.[19] Screening of such large numbers of nonimmigrants, even from selected countries with high rates of tuberculosis, would be impractical to implement, very costly, and, unless performed just prior to flying, would not necessarily prevent exposures to persons with active tuberculosis on aircraft from occurring.

To develop recommendations based on the available scientific evidence, in February, 1995, CDC met with representatives from the Federal Aviation Administration (FAA), Air Transport Association (ATA), Council of State and Territorial Epidemiologists (CSTE), National Tuberculosis Controllers Association, and medical consultants from major airline companies. In March, 1995, CDC summarized six investigations into the possibility of *M.tuberculosis* transmission on aircraft and provided guidance for the notification of passengers and flight crew if an exposure to tuberculosis occurs during travel on commercial aircraft.[2] Four investigations found no conclusive evidence that transmission of *M.tuberculosis* to other passengers occurred.[2,20,21] Table 4 includes suggested criteria and procedures for notification of contacts which were distributed to airline companies, state health departments, and tuberculosis control programs nationally in March, 1995. The decision to notify passengers and crew potentially exposed to tuberculosis should be guided by three criteria: flight duration, infectiousness of the index case (e.g., smear-positive, cavitary pulmonary tuberculosis,

laryngeal tuberculosis, or documented transmission to contacts), and seating proximity to the index case, depending on the aircraft design.[2] In cases where the airline is informed first, the airline should provide the name of the passenger's physician to the state health department in the state where the patient resides or is being treated for tuberculosis so that the health department may make a determination of infectiousness. Application of these criteria to instances of exposure to tuberculosis on aircraft will facilitate informing those members of the public who may potentially benefit from preventive therapy, yet avoid expenditure of resources in circumstances where *M. tuberculosis* transmission is highly unlikely. The top priority of tuberculosis control programs remains identifying and ensuring complete treatment of all active tuberculosis cases.[22]

These suggested procedures apply to all domestic and foreign-based airline carriers. However, they were developed in the context of tuberculosis control in the United States and may not be directly applicable to countries where tuberculosis prevention and control strategies are different. The World Health Organization Global Tuberculosis Programme, in collaboration with CDC, has made these suggested procedures available to non-U.S.- based carriers through the International Airline Transportation Association.

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Table 1. Results of Tuberculin Skin Tests for the 760 Passengers and Crew Members, According to Flight.*

Tuberculin skin test result	Flight 1 (n=298)	Flight 2 (n=104)	Flight 3 (n=109)	Flight 4 (n=249)	Total (n=760)
Total positive	7 (2.3)	4 (3.8)	3 (2.8)	15 (6.0)	29 (3.8)
Prevalent positive†	7 (2.3)	4 (3.8)	3 (2.8)	9 (3.6)	23 (3.0)
Conversion	0	0	0	6 (2.4)	6 (0.8)
Negative‡	291 (97.7)	100 (96.2)	106 (97.2)	234 (94.0)	731 (96.2)

***** Flight 1 was from Honolulu to Chicago in April, flight 2 from Chicago to Baltimore in April, flight 3 from Baltimore to Chicago in May, and flight 4 from Chicago to Honolulu in May.

† These contacts had no results of previous skin tests in their medical records.

‡ All 10 contacts who were exposed on two connecting flights had negative tuberculin skin tests.

Table 2. Characteristics of the Passengers and Crew Members on Flight 4 Who Had Positive Tuberculin Skin Tests.

Contact No.	Age (yr)	Race or Ethnic Group*	Sex	Rows from Index Patient	Tuberculin skin test		Risk Factors†	Infection Status‡
					First (mm)	Second (mm)		
1	55	W	M	49	10	—	Uncle with tuberculosis	Previous
2	43	A	M	31	11	—	Foreign-born	Previous
3	76	W	M	26	10	—	Lived in Southeast Asia	Previous
4	30	W	M	24	4	18	Friend with tuberculosis	Previous
5	28	W	F	24	20	—	Friend with tuberculosis, health care worker	Previous
6	57	W	M	13	0	20	Foreign-born	Previous
7	51	W	F	13	18	—	Foreign-born	Previous
8	55	W	F	13	0	11	None identified	New
9	37	W	F	12	0	12	None identified	New
10	38	A	M	9	14	—	Foreign-born, received BCG	Previous
11	29	H	M	6	20	—	Foreign-born, received BCG	Previous
12	47	W	F	2	11	—	None identified	New
13	41	W	M	1	0	15	None identified	New
14	36	W	M	1	0	19	None identified	New
15	41	W	M	0	17	—	None identified	New

* W denotes white, A Asian, and H Hispanic.
† Foreign-born denotes birth in a country where the rate of tuberculosis is at least 10 times higher than in the United States and where bacille Calmette-Guérin (BCG) vaccine is routinely used.
‡ The investigators' determinations were based on the results of the skin tests and on the risk factors.

Table 3. Seating Locations in Aircraft and Results of Tuberculin Skin Tests of Passengers and Crew Members on Flight 4 Who Had No Risk Factors.*

Seat Location	No. with Positive Skin Test/No. Tested (%)	Rate Ratio (95% CI)†	P Value
Not same cabin section as index patient	0/136	Reference value	—
Same cabin section as index patient	6/68 (8.8)	Undefined	0.001
Within 2 rows	4/13 (30.8)	8.5 (1.7–41.3)	0.01
Elsewhere in same section	2/55 (3.6)	Reference value	

* Data for the flight crew exclude seven flight attendants who could not recall their work assignments on Flight 4; all had negative tuberculin skin tests. Risk factors for a positive tuberculin skin test included having been born or having lived in a country where the rate of tuberculosis is at least 10 times higher than in the United States,[7] having had possible occupational exposure, having received the bacille Calmette-Guérin vaccine, or having had exposure to a family member or friend with tuberculosis.

† CI denotes confidence interval.

Table 4. Suggested criteria and procedures for notification of passengers and flight crew following exposure to tuberculosis on commercial aircraft.

1. Once the health department has determined that a passenger with tuberculosis was likely to be infectious at the time of the flight,[2] the airline company should be consulted to verify that the person with tuberculosis was on the flight in question and the flight duration.

2. Health departments and airline medical consultants may consider limiting notification to flights of greater than eight hours duration. Health departments may consider shorter flights for patients considered to be particularly infectious, such as laryngeal tuberculosis, which has been reported to result in transmission after only five hours of classroom exposure.[23]

3. Depending on aircraft design, notification of only those passengers seated and crew working in the same cabin area as the person with tuberculosis may be adequate. Collaboration between the health department and airline is essential to determine who should be notified and how notification will occur.

4. Written notification of passengers and flight crew should be done by the airline in cooperation with the health department.

Figure 1. Chest film of index case taken 8 days after Flight 4 showing extensive bilateral pulmonary disease with cavitary lesions. (Not available in electronic format.)

Figure 2. Diagram of Boeing 747-100 with seat assignment of tuberculin skin test positive passengers and crew on Flight 4. Numbers refer to contacts listed in Table 2. (Not available in electronic format.)